

Message

From: Jon Urban [jurban@toxstrategies.com]
Sent: 4/6/2018 8:11:06 PM
To: Jacobs, Keith [jacobs.keith@epa.gov]
Subject: SOT Follow-up - TCE RoB poster and paper
Attachments: Poster 8-2018-Urban-PRINT.pdf; Wikoff et al Int J Toxicol 2018 .pdf; Harris et al Toxicol Lett 2018.pdf

Keith,

It was a pleasure to make your acquaintance at SOT a few weeks ago. As a follow-up to our discussion on TCE-CHD risk and your request, I have attached the poster I presented that Wednesday as well as the published paper (Wikoff et al., 2008; this just went to print this month).

I have also attached the recently published chick TCE-CHD MOA paper I had mentioned during our discussion (Harris et al., 2018). If you recall, this group is advancing the hypothesis that TCE induces CHDs only at low exposure levels *in utero*. The investigators report an association between *in ovo* TCE exposure and HNF4a expression in the hearts. They do attempt to provide a phenotypic anchor for their data (report decrease in fetal cardiac output in the chick eggs), although the graph of these functional results (Fig 6) indicates notable variability in measuring cardiac output (i.e., setting aside the need for multiple control groups, there is considerable difference between the two control groups to suggest the treatment group results are less certain than reported).

In addition, ResearchGate indicates this lab has also recently submitted another MOA TCE-CHD paper for publication titled "HNF4a transcription is a target of trichloroethylene toxicity in the embryonic mouse heart". It hasn't been accepted anywhere yet as far as I can tell (at least it's not indexed in PubMed or EMBASE) but it appears to report similar mechanistic data in mice exposed to TCE *in utero*. It will be interesting to see if they actually looked for CHDs in this mouse model, as no mouse study to date has reported TCE-induced CHDs.

I hope this helps you and your team in your assessment. Please feel free to contact me if you have any questions about our RoB evaluation.

Best regards,

Jon

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